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(54) Title: PROCESS OF PREPARATION OF VALACYCLOVIR AND RELEVANT INTERMEDIATES

(57) Abstract

Process of preparation of valacyclovir (I), wherein derivative (IV) of acyclovir (I), in which the OH group of acyclovir at the omega position has been replaced by a good leaving group Z, is reacted with an alkaline salt of L-valine (V), to give intermediate (VI), which is successively hydrolyzed in an acid medium to give the corresponding salified valacyclovir (I-A), which may be optionally transformed into valacyclovir (I).

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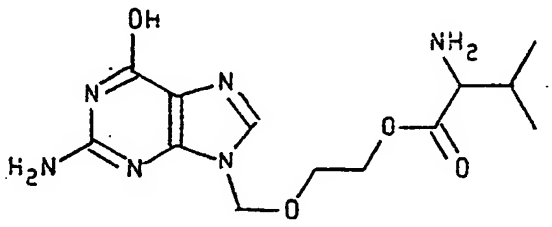
Process of preparation of valacyclovir and relevant intermediates

Field of the invention

The present invention relates to a process of preparation of valacyclovir and relevant intermediates.

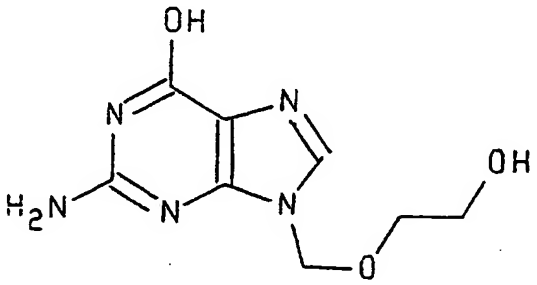
State of the art

Valacyclovir, i.e. 2-[(2-amino, 1,6-dihydro, 6-oxo, 9-H, purin-9-yl)methoxy]ethyl, L-valinate of formula (I)



(I)

is the ester of acyclovir, i.e. of 2-amino, 1,6-dihydro-6-oxo, 9-H, 9[(2-hydroxyethoxy)methyl]purine of formula (II) with L-valine.



(II)

Said substance, which is hydrolyzed to acyclovir by the body, may be administered by the oral way.

Several esters of acyclovir with amino acids are reported to be effective "prodrugs" of acyclovir; among them, the ester with L-valine is the most absorbable and, therefore, provides high acyclovir

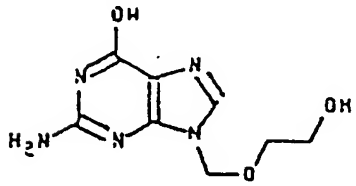
concentrations in the body.

The use of valacyclovir produces acyclovir concentrations in the plasma equivalent to those obtained by i.v. administration. the antiviral activity of acyclovir and its efficacy over a broader spectrum of herpetic infections being thus increased.

European Patent 0 308065 B1 describes valacyclovir and in particular the two processes of preparation of said active ingredient reported below:

1) condensation of acyclovir with N-benzyloxycarbonyl valine in the presence of a condensing agent, such as dicyclohexylcarbodiimide, and successive removal of the protecting group by hydrogenolysis, i.e. according to the following scheme (1)

Scheme 1

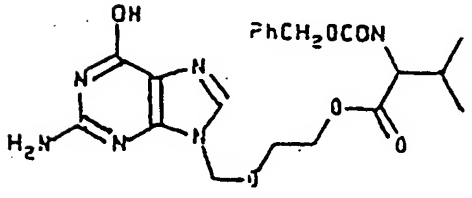


II

CBZ-L-Valina

DMAP

DCC



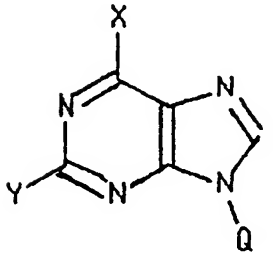
H_2

Pd/C

I

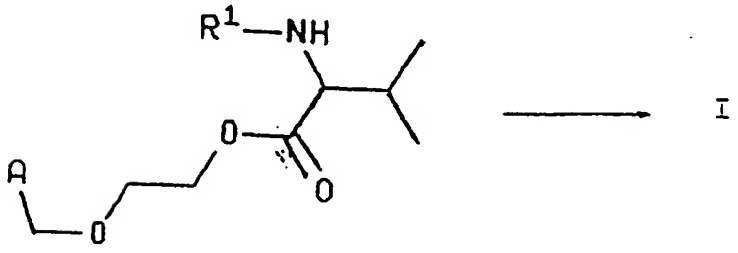
2) condensation of guanine (III), in which X is a protecting group of the hydroxyl function, Q is H, an acetyl, benzoyl or trimethylsilyl group, with the product of formula $ACH_2OCH_2CH_2OCH(NHR^1)CH(CH_3)_2$, in which A is a leaving group, such as a halogen atom (Br or Cl), acetate or benzoate, R^1 is a protecting group of the aminic function, i.e. according to the following scheme (2)

Scheme 2



+

III



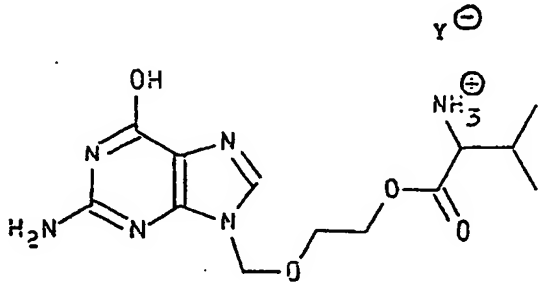
I

There are several drawbacks to the aforesaid processes: actually they require very costly reactants, such as benzyloxy carbonyl chloride, dicyclohexylcarbodiimide, palladium for hydrogenation, as well as specific plants, such as a pressure hydrogenator, which conditions prevent the aforesaid processes from being easily scaled up to industrial size.

Therefore, the need for a process of synthesis allowing the obtainment of high-purity valacyclovir in high yields, free from the drawbacks of the processes known in the prior art and easily scaled up to commercial size was deeply felt.

Summary

It has surprisingly been found a process of preparation of high-purity valacyclovir of formula (I) or of a salt thereof of formula (I-A), in high yields.

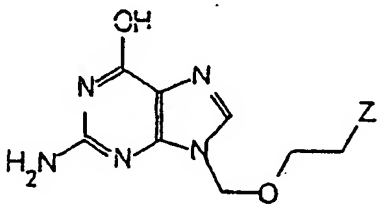


(I-A)

in which $Y^{\ominus}$ is selected from the group consisting of $Cl^{\ominus}$, $HSO_4^{\ominus}$, para-toluenesulfonate, methanesulfonate, trifluoromethane-sulfonate, free from the drawbacks of the processes known and, therefore, easily scalable to industrial dimensions.

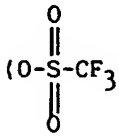
In particular, the process of the present invention comprises the following steps:

a) reacting acyclovir (II) with a Z-L reactant selected from the group consisting of para-toluenesulfonyl chloride, methanesulfonyl chloride, trifluoromethanesulfonyl chloride, triflic anhydride, sulfuryl chloride, phosphorus tribromide and trichloride, in the presence of a base neutralizing the acidity that forms during the reaction, thereby obtaining a compound of formula (IV)



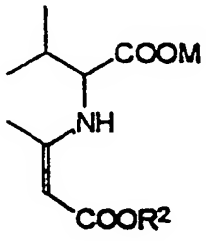
(IV)

in which Z is selected from the group consisting of para-toluenesulfuryl (O-Tosyl), methanesulfuryl (O-mesyl), trifluoromethanesulfuryl



(O-S-CF_3), Cl, Br;

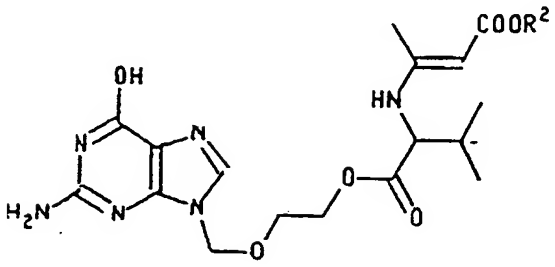
b) reacting product (IV) coming from the preceding step with an alkaline salt of valine of formula (V)



(V)

in which R^2 is a C_1-C_{10} alkyl and M is an alkali metal.

in the presence of a dipolar aprotic high-boiling solvent or a high-boiling ether, at a temperature ranging from 20°C to 150°C, to give ester (VI)



(VI)

in which R^2 has the above meanings;

c) transforming product (VI) coming from the preceding step into the corresponding valacyclovir hydrochloride (I-A) by acid hydrolysis with a strong acid of mineral or organic type, at a temperature ranging from 0°C to 50°C, in water and/or in an organic solvent selected from the group consisting of the solvent used in step (b), an alcohol containing 1 to 4 carbon atoms, an ether, and a mixture of said alcohol and said ether;

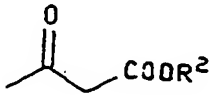
d) optionally converting valacyclovir hydrochloride (I-A) into the corresponding free base (I) by conventional methods.

In particular, it has surprisingly been found that, in step (a) of the process according to the present invention, product (IV) is selectively formed in high yields, whereas there is no formation of by-products deriving from the possible reaction of the Z-L reactant with the aminic group at the 2 position and/or with the hydroxyl at the 6 position of the purinic ring.

Also, this invention extends to intermediates (IV) and (VI) obtained

by the process according to the present invention.

The present invention also relates to an alkaline salt of L-valine (V), in which M has the above meanings, used as a reactant in step (b) of the process of the present invention, and the relevant process of synthesis, which, in particular, includes the reaction of L-valine in the presence of an alkyl acetatoacetate of formula (VII)



(VII)

in which R^2 has the above meanings, in a solvent selected from among an alcohol containing 1 to 4 carbon atoms, a ketone or an aromatic hydrocarbon.

Description of the figures

Fig. 1 shows the I.R. spectrum, run KBr, containing 1% of hydrated valacyclovir hydrochloride (I-A) prepared as described in Examples 6 and 9.

Fig. 2 shows the I.R. spectrum, run KBr, containing 1% of anhydrous valacyclovir hydrochloride (I-A) prepared as described in Example 11.

Detailed description of the invention

The base preferably used in step (a) of the process according to the invention is selected from potassium carbonate, sodium methylate and pyridine.

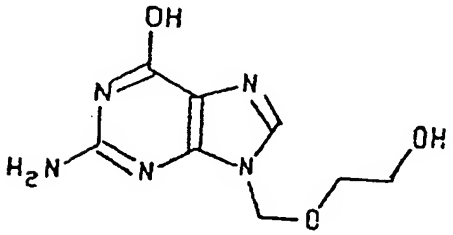
The solvent used in step (a) is preferably N,N-dimethylformamide or dimethylsulfoxide or pyridine.

According to particularly preferred embodiments, pyridine or a pyridine-dimethylformamide mixture is used in step (a) as a solvent or as a base.

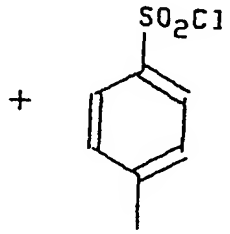
According to a particularly preferred embodiment, para-toluenesulfonyl chloride or methanesulfonyl chloride is used in step (a) as a Z-L reactant.

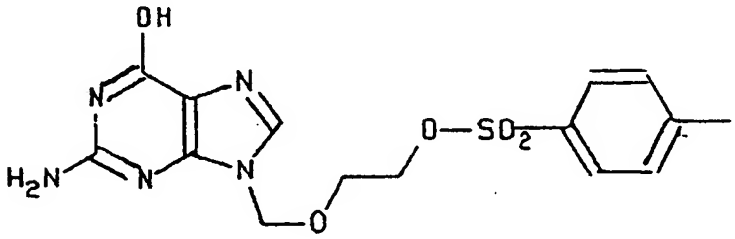
Should para-toluenesulfonyl chloride be used as a Z-L reactant, the process of the present invention will proceed according to Scheme 3

Scheme 3

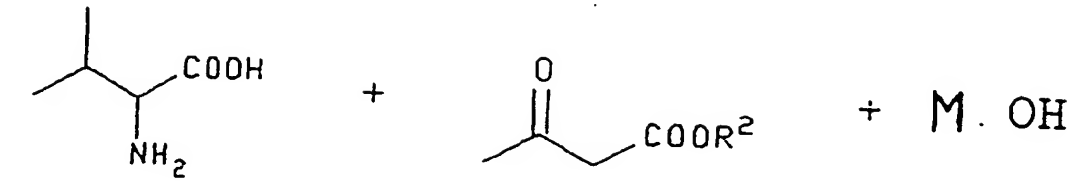


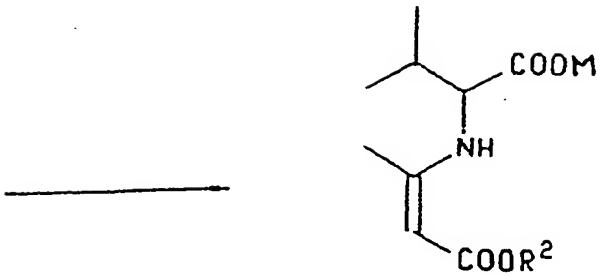
(II)



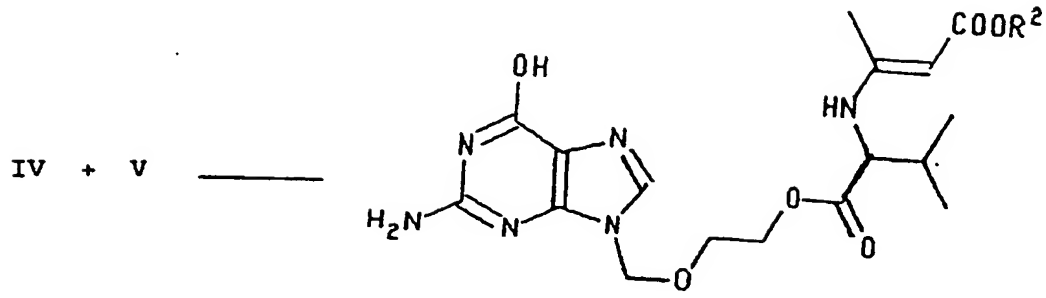


(IV)

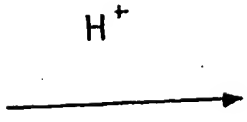

COOH
NH2
+
O
COOR2
+ M. OH


COOM
NH
COOR2

(V)


IV + V
OH
N
N
H2N
N
N
HN
COOR2
O
O
O

(VI)


H+
I

In step (a), omega-chloroacyclovir may be obtained not only by reacting acyclovir with PCl_3, but also by treating omega-tosyl or mesyl acyclovir in the presence of LiCl.

When a dipolar aprotic solvent is used in step (b) according to the present invention, said solvent is preferably N,N-dimethylformamide or dimethylsulfoxide.

When an ether high-boiling i.e. boiling at temperatures ≥ 100°C is used in step (b), said ether is preferably dioxane or diglyme.

Step (b) is preferably carried out at a temperature ranging from 70°C to 90°C.

In step (b), when the reactant used is intermediate (IV), in which Z=Cl (omega-chloroacyclovir), a further reactant, i.e. potassium iodide, is added.

Product (VI), recovered from the reaction mixture, can be used in successive step (c) without purification.

When a mineral strong acid is used in step (c) of the claimed process, said acid is preferably sulfuric acid or hydrochloric acid. When, in said step, an organic strong acid is used, this is preferably para-toluenesulfonic acid or methanesulfonic acid or trifluoromethanesulfonic acid. In this step, the acid may be added either in stoichiometric or catalytic amounts.

According to a particularly preferred embodiment, the aforesaid acid is added in quantities securing constant pH values of 2 to 3.

When, in step (c), an alcohol containing 1 to 4 carbon atoms is used as a solvent, said alcohol is preferably methanol. Instead, when an ether is used, said ether is preferably dioxane or tetrahydrofuran. When a mixture of the aforesaid organic solvents is used, said mixture

preferably consists of methanol and tetrahydrofuran.

According to a particularly preferred embodiment, step (c) is directly conducted on the reaction mixture obtained in (b), i.e. in the presence of the same solvent as used in (b), without isolating intermediate (VI). Valacyclovir may be used as an active ingredient in the form of a salt (I-A), preferably the hydrochloride salt, or may be transformed, according to conventional techniques, into the corresponding free base (I), as envisaged in step (d) of the present invention.

In particular, valacyclovir hydrochloride exists in two crystalline modifications identified by different I.R. spectra (Fig. 1 and, respectively, Fig. 2).

A crystalline modification may have a water content that varies from 2% to 10% with the atmospheric moisture content. The other has a low water content (lower than 2%), which does not significantly change by exposure to atmospheric moisture.

Either one of the two modifications is obtained depending on the operating conditions, in particular on the water content of the crystallization solvents.

According to a particularly preferred embodiment, step (d) includes the addition of an ammonium hydroxide aqueous solution to a valacyclovir hydrochloride solution (I-A) to adjust the pH to a constant value ranging from 9 to 9.5.

Particularly preferred alkaline salts of L-valine (V) according to the present invention are those in which M is sodium and/or potassium and R^2 is methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl.

Should their formation take place in a short-chain alcohol, this will

preferably be methanol; should it take place in a ketone, this will preferably be methylethylketone or diethylketone or methylisobutylketone; should it take place in an aromatic hydrocarbon, this will preferably be toluene or xylene.

In the process of preparation of the alkaline salt according to the present invention, an alkyl acetoacetate (VII), in which R^2 is preferably methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, is used.

The following examples only illustrate the process of preparation of valacyclovir according to the invention as well as the process of preparation of the corresponding L-valine alkaline salt (V).

Example 1 - L-valine sodium salt (V)

A 500-ml four-neck flask, equipped with mechanical stirrer, thermometer, reflux with calcium chloride valve and inlet for nitrogen, was fed, at room temperature and under a nitrogen stream, with 110 ml methylethylketone and 10 g L-valine.

The resulting suspension was added with 10.1 ml methyl acetoacetate and 3.52 g NaOH (99%) under stirring at room temperature and under a nitrogen stream. No solution was obtained.

The reaction mixture was heated to reflux (78°C-80°C) for 3 h (a complete solution was obtained already at 50°C), and then concentrated in a rotating evaporator by means of water vacuum. Solvent traces were first removed by toluene addition to the residue followed by solvent distillation under vacuum and then by treatment of the residue with ethyl ether followed by solvent distillation in a rotating evaporator under water vacuum.

The residue obtained was treated with 200 ml ethyl ether, filtered

through a Buchner funnel and washed with fresh ethyl ether.

The hygroscopic solid obtained was mashed and recrystallized from hexane (200 ml) at room temperature.

18.7 g of product was obtained (yield 92.5%).

Perchloric acid grade: 93.9%.

Water content (KF): 5.6%.

The ^1H NMR spectrum of the compound showed signals at δ 0.85 (6H.t); 1.80 (3H.s); 2.00 (1H.m); 3.45 (3H.s); 3.50 (1H.m); 4.20 (1H.s); 8.85 (1H.d).

Example 2 - L-valine potassium salt (V)

A 500-ml four-neck flask, equipped with mechanical stirrer, thermometer, reflux with calcium chloride valve and dropping funnel, was fed at room temperature with 240 ml methanol and 10 g L-valine. No solution was obtained.

5.1 g KOH (92%) dissolved in 100 ml methanol were added dropwise at room temperature, under a nitrogen stream. The mixture was heated to boiling. A complete solution was obtained, kept at that temperature for 45 min and then allowed to cool to 25°C-30°C. At that temperature and under a nitrogen stream, 10.3 ml methyl acetoacetate dissolved in 20 ml methanol were added dropwise. The resulting mixture was heated to reflux and kept at that temperature for 2 h. Methanol was removed under water vacuum to give a doughy residue, which was dissolved with acetone until formation of a crystalline solid, which was filtered through a Buchner funnel and 25 oven dried at 50°C.

16.20 of a hygroscopic solid was obtained (yield 75%).

Example 3 - L-valine sodium salt (V)

A 100-ml flask, equipped with mechanical stirrer and reflux, was fed at room temperature with 3 g L-valine, 25 ml toluene and 2.05 g aqueous NaOH at 50%. The mixture was stirred for 30 min at 50°C and then added with 3.1 g methyl acetoacetate. The reaction mixture obtained was stirred for 30 min at 50°C, heated to reflux and kept at that temperature for 15 min. The product was recovered after removing the reaction solvents in a rotating evaporator under water vacuum three times, each time adding 50 ml fresh toluene. 6.3 g of product was obtained (yield 99%).

Example 4 - omega-Tosyl acyclovir (IV)

A 250-ml four-neck flask, equipped with mechanical stirrer, thermometer, reflux with calcium chloride valve and inlet for nitrogen, was fed at room temperature with 10 g acyclovir in 60 ml pyridine. No solution was obtained.

At that temperature and under a nitrogen stream, the flask was fed with 15 g para-toluenesulfonyl chloride. The mixture was stirred at room temperature and the product slowly passed into solution. The reaction was exothermic and the highest temperature reached was 55°C; thus the reaction mixture spontaneously heated up to 50°C-55°C until reaction completion. (Overall reaction time: approx. 90 min).

The reaction was followed by TLC. After the reaction was complete, the mixture was cooled to 20°C and poured into 300 ml iced water. The pale yellow precipitated solid was filtered and washed with water.

The solid obtained was suspended in water (pH 7.2) and brought to pH 5.0 by addition of 15% HCl, while the temperature was kept at 0°C-5°C. The suspension was filtered through a Buchner funnel and the precipitate obtained was washed with water and oven dried at 45°C-50°C

for 3 h.

14.8 g of a pale yellow solid was obtained (yield 87.9%).

The mass spectrum of the compound showed peaks at m/z: 379 (molecular ion), 207 (para-toluenesulfonic acid loss), 164 ($-O-CH_2CH_2-OTs$ fragment loss), 155 ($CH_3-Ph-SO_2$ fragment), 150 ($CH_2-O-CH_2CH_2-OTs$ loss).

The ^1H NMR spectrum of the compound showed signals at δ 2.4 (3H,s); 3.6 (2H,m); 4.1 (2H,m); 5.28 (2H,s); 6.5 (2H,bs) (disappears by deuteration); 7.43 (2H,m); 7.72 (2H,m); 7.76 (1H,s).

Example 5 - Ester (VI)

A 500-ml four-neck flask, equipped with mechanical stirrer, thermometer, reflux with calcium chloride valve and inlet for nitrogen, was fed at room temperature with 10 g omega-tosyl acyclovir prepared as described in Example 4, 180 ml DMF, 7.5 g L-valine sodium salt (V) prepared as described in Example 1. The mixture was heated to 80°C for 3 h. The reaction was followed by TLC.

After the reaction was complete, the reaction mixture was concentrated in a rotating evaporator by means of an oil pump until obtaining a volume residue of 30 ml (rotating evaporator bath temperature of 70°C).

The mixture was added dropwise to 300 ml iced water, while the temperature was kept at 0°C-5°C, filtered through a Buchner funnel, washed 3 times with 50 ml water, and oven dried at 50°C. 8.5 g of product was obtained (yield 80%).

The mass spectrum of the compound showed signals at m/z: 422 (molecular ion), 308 ($-NH-C(CH_3)=CH-COOCH_3$ fragment loss), 164 (9-methylene guanine fragment), 151 (guanine fragment).

The ^1H NMR spectrum of the compound showed signals at δ 0.85 (6H.m); 1.82 (3H.s); 2.02 (1H.m); 3.3 (3H.s); 3.68 (2H.m); 4.06 (1H.m); 4.16 (1H.m); 4.24 (1H.m); 5.32 (2H.s); 6.3 (2H.bs) (disappears by deuteration); 7.8 (1H.s); 8.82 (1H.d).

Example 6 - Hydrated valacyclovir hydrochloride (I-A)

A 250 ml conical flask equipped with magnetic stirrer was fed at 20°C with 4 g ester (VI) prepared as described in Example 5, in 40 ml methanol and 40 ml tetrahydrofuran. The mixture was added under stirring with 15% HCl until the solution pH was 2.0, kept at 20°C for approx. 3 h, while the pH was adjusted to a constant value ranging from 2.0 to 2.5 by addition of 15% HCl. The reaction was followed by TLC. After the reaction was complete, the reaction mixture was concentrated in a rotating evaporator under water vacuum and the residue was dissolved in 75 ml ethanol. The mixture was heated under stirring to 50°C for 30 min, allowed to cool to 0°C for 1 h, filtered, and washed with ethanol. The wet product was dried under vacuum. 2.8 g of product (I-A) having a water content of 5% was obtained (reaction yield 78% of theoretical value).

The I.R. spectrum of the product is shown in Fig. 1.

The mass spectrum of the compound showed peaks at m/z: 324 (molecular ion of the base), 281 ($CH(CH_3)_2$ fragment loss), 209 (-OCOCH-$(NH_2)CH(CH_3)_2$ fragment loss), 164 (9-methylene guanine), 151 (guanine fragment).

The ^1H NMR spectrum of the compound showed signals at δ 0.86 (6H.m); 2.07 (1H.m); 3.7 (2H.m); 4.18 (1H.m); 4.36 (1H.m); 5.36 (2H.s); 6.66 (2H.bs) (disappears by deuteration); 7.8 (1H.s).

Example 7 - Valacyclovir base (I)

A solution of 0.5 g valacyclovir hydrochloride, prepared as described in Example 6, in 25 ml distilled water was added with 12.5% ammonium hydroxide until the solution pH was brought to a constant value of 9.0-9.5.

The resulting mixture was concentrated under vacuum at 50°C to a volume of 10 ml. After cooling, the precipitate was filtered and dried.

273 mg of a white product having the same analytical characteristics as those of a sample obtained according to European Patent 0308 056 B1 was obtained.

The mass spectrum of the compound showed peaks at m/z: 324 (molecular ion), 281 ($CH(CH_3)_2$ fragment loss), 209 ($-OCO-CH(NH_2)CH(CH_3)_2$ fragment loss), 164 (9-methylene guanine fragment), 151 (guanine fragment).

The ^1H NMR spectrum of the compound showed signals at δ 0.74 (3H,d); 0.80 (3H,d); 1.72 (1H,m); 3.05 (1H,d); 3.66 (2H,m); 4.08 (1H,m); 4.15 (1H,m); 5.32 (2H,s); 6.50 (2H,bs) (disappears by deuteration); 7.8 (1H,s).

Example 8 - omega-mesyl acyclovir (IV)

A 250 ml flask was fed with 30 ml pyridine, 30 ml DMF and 10 g acyclovir. The mixture was cooled to 0°C, added dropwise during 30 min with 6.1 g methanesulfonyl chloride, stirred for 3 h, and then gradually heated to 20°C. TLC analysis showed that the reaction was complete. The mixture was added with 250 ml water and ice. A few minutes later, an abundant precipitate was formed, which was filtered, washed with water and dried at 50°C.

9.6 g of omega-mesyl acyclovir was obtained (yield 70.9%).

Example 9 - Hydrated valacyclovir hydrocloride (I-A)

A 100 ml conical flask equipped with magnetic stirrer was fed with 10 ml DMF, 1 g omega-mesyl acyclovir prepared as described in Example 8 and 0.935 g L-valine sodium salt (V) prepared as described in Example 1.

The reaction mixture was stirred at 80°C for 3 h. After that time, TLC analysis showed the disappearance of the spot corresponding to omega-mesyl acyclovir.

The solution pH was brought to 2.0-2.5 by addition of 15% HCl at 20°C. TLC analysis showed the appearance of the spot corresponding to valacyclovir.

The mixture was concentrated under vacuum and the doughy residue was dissolved in 5 ml absolute ethanol and cooled to 0°C.

The crystalline precipitate was filtered, washed with little ethanol and dried.

0.72 g of valacyclovir hydrochloride having a water content of 6.5% was obtained (reaction yield 57% of theoretical value)

The I.R. spectrum of the product is shown in Fig. 1.

The ^1H NMR and mass spectral data are identical with those of the product obtained in Example 6.

Example 10 - omega-Chloroacyclovir (IV)

A 100 ml conical flask was fed with 10 ml DMF, 1.0 g omega-mesyl acyclovir and 0.5 g lithium chloride. The mixture was heated to 60°C under a nitrogen stream. Three hours later, TLC analysis showed that the reaction was complete. The solution was cooled to 20°C, poured into 100 ml water, stirred for 10 min, filtered and washed with water. After drying at 50°C, 0.77 g of product was obtained (yield 96% of theoretical value).

The mass spectrum of the compound showed peaks at m/z: 243 (molecular ion). 208 (chlorine loss). 180 (CH_2CH_2Cl fragment loss). 164 (-O-CH_2CH_2-Cl fragment loss).

The ^1H NMR spectrum of the compound showed signals at δ 3.65-4.76 (4H.m); 4.40 (2H.s); 6.54 (2H.s) (disappears by deuteration); 7.82 (1H.s); 10.54 (1H.s) (disappears by deuteration).

Example 11 - Anhydrous omega-valacyclovir hydrochloride (I-A)

A 25 ml conical flask was fed with 1.0 g omega-chloroacyclovir, 10 ml DMF, 1.0 g L-valine sodium salt (V). The mixture was heated to 80°C, added portionwise (one portion of approx. 100 mg every 30 min) with 0.5 g potassium iodide, allowed to stir at 95°C overnight, then cooled to 20°C and poured into 50 ml water at 15°C.

The precipitate was filtered and washed with 2x5 ml water.

The wet solid was suspended in 10 ml methanol, stirred at 15°C-20°C and brought to pH 2 by addition of 15% HCl. The resulting solution was concentrated to small volume and diluted with 10 ml isopropanol.

The solid obtained was filtered, recrystallized twice from methanol and dried.

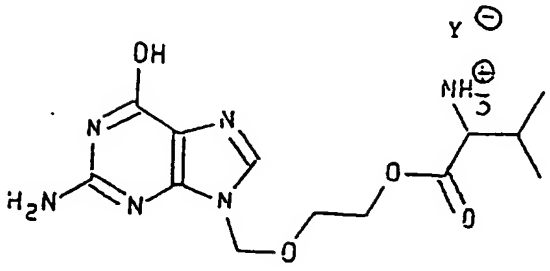
1 g of valacyclovir hydrochloride having a water content of 0.4% was obtained (reaction yield 68% of theoretical value).

The I.R. spectrum of the product is shown in Fig. 2.

H^1 NMR and mass spectral data are identical with those of the product obtained in Example 6.

Claims

1 1. Process of preparation of salified valacyclovir (I-A)

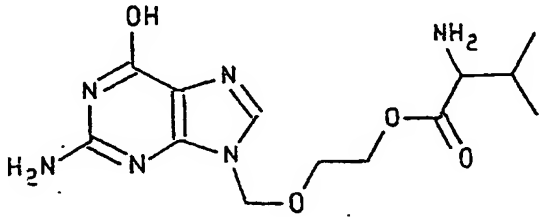


(I-A)

2 in which $Y^{\ominus}$ is selected from the group consisting of $Cl^{\ominus}$, $HSO_4^{\ominus}$, para-

3 toluenesulfonate, methanesulfonate, trifluoromethane-sulfonate or the

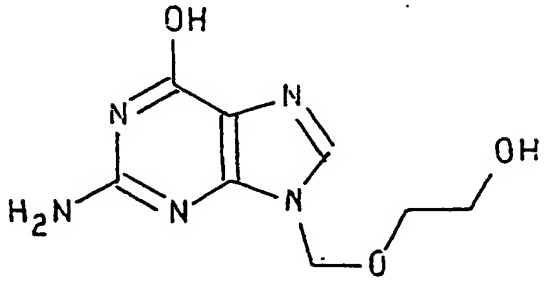
4 corresponding free base (I)



(I)

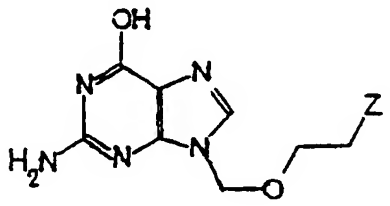
5 consisting of the following steps:

6 a) reacting acyclovir (II)



(II)

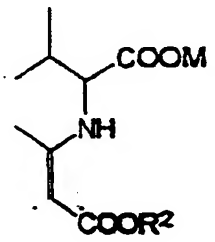
with a Z-L reactant selected from the group consisting of para-toluenesulfonyl chloride, methanesulfonyl chloride, trifluoromethanesulfonyl chloride, triflic anhydride, sulfuryl chloride, phosphorus tribromide and trichloride, in the presence of a base, to give a compound of formula (IV)



(IV)

in which Z is selected from the group consisting of para-toluenesulfuryl, methanesulfuryl, trifluoromethanesulfuryl, Cl, Br;

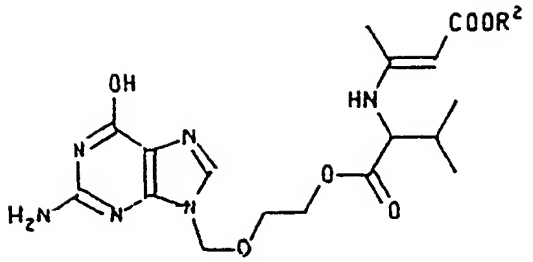
b) reacting product (IV) coming from the preceding step with an alkaline salt of L-valine of formula (V)



(V)

in which R^2 is a C_1-C_{10} alkyl and M is an alkali metal,

in the presence of a high-boiling organic solvent selected from the group consisting of a dipolar aprotic solvent and an ether, at a temperature ranging from 20°C to 150°C, to give ester (VI)



(VI)

in which R^2 has the above meanings;

c) transforming product (VI) coming from the preceding step into the corresponding salified valacyclovir (I-A) by acid hydrolysis with a strong acid of mineral or organic type, at a temperature ranging from 0°C to 50°C, in water and/or in an organic solvent selected from the group consisting of the solvent used in step (b), an alcohol containing 1 to 4 carbon atoms, an ether, and a mixture of said alcohol and said ether;

d) optionally converting salified valacyclovir (I-A) coming from the preceding step into the corresponding free base (I) by conventional methods.

2. The process as claimed in claim 1, wherein the base used in step (a) is selected from the group consisting of potassium carbonate, sodium methylate and pyridine.

3. The process as claimed in any preceding claim, wherein the solvent used in step (a) is selected from the group consisting of N,N-dimethylformamide, dimethylsulfoxide, pyridine.

4. The process as claimed in any of claims 1 and 2, wherein pyridine or a pyridine-dimethylformamide mixture is used in step (a) as a solvent or as a base.

5. The process as claimed in any of claims 1 to 4, wherein para-

toluenesulfonyl chloride or methanesulfonyl chloride is used in step (a) as a Z-L reactant.

6. The process as claimed in any of claims 1 to 5, wherein, when a dipolar aprotic solvent is used in step (b), said solvent is selected from the group consisting of N,N-dimethylformamide and dimethylsulfoxide.

7. The process as claimed in any of claims 1 to 5, wherein, when a high-boiling ether is used in step (b), said ether is selected from the group consisting of dioxane and diglyme.

8. The process as claimed in any of claims 1 to 7, wherein step (b) is carried out at a temperature ranging from 70°C to 90°C.

9. The process as claimed in any of claims 1 to 7, wherein, when the reactant used in step (b) is intermediate (IV), in which Z=Cl, a further reactant, i.e. potassium iodide, is added.

10. The process as claimed in any of claims 1 to 9, wherein, when a mineral strong acid is used in step (c), said acid is selected from the group consisting of sulphuric acid and hydrochloric acid.

11. The process as claimed in any of claims 1 to 9, wherein, when an organic strong acid is used in step (c), said acid is selected from the group consisting of para-toluenesulfonic acid, methanesulfonic acid and trifluoromethanesulfonic acid.

12. The process as claimed in any of claims 1 to 11, wherein the aforesaid acid is added in quantities securing constant pH values of 2 to 3.

13. The process as claimed in any of claims 1 to 12, wherein, when an alcohol containing 1 to 4 carbon atoms is used as a solvent in step (c), said alcohol is preferably methanol.

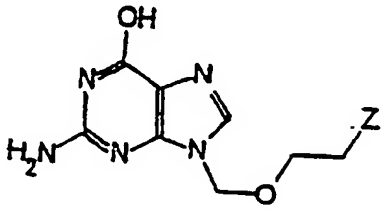
14. The process as claimed in any of claims 1 to 12, wherein, when an ether is used as a solvent in step (c), said ether is selected from the group consisting of dioxane and tetrahydrofuran.

15. The process as claimed in any of claims 1 to 12, wherein, when a mixture of an alcohol and of an ether is used in step (c), said mixture consists of methanol and tetrahydrofuran.

16. The process as claimed in any of claims 1 to 12, wherein step (c) is directly conducted on the reaction mixture obtained in (b), i.e. without isolating intermediate (VI).

17. The process as claimed in any of claims 1 to 16, wherein step (d) includes the addition of an ammonium hydroxide aqueous solution to salified valacyclovir (I-A) solution to adjust the pH to a constant value ranging from 9 to 9.5.

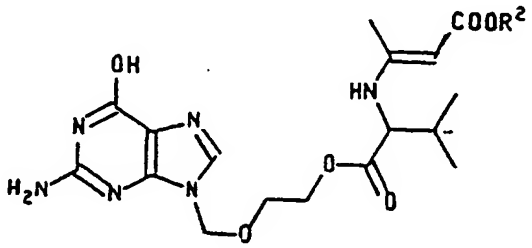
18. Substituted omega-acyclovir derivative of formula (IV)



(IV)

in which Z is selected from the group consisting of para-toluenesulfuryl, methanesulfuryl, trifluoromethanesulfuryl, Cl, Br.

19. Acyclovir ester of formula (VI)

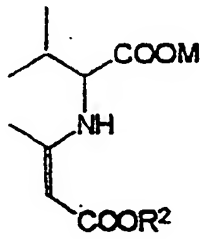


(VI)

in which R^2 is C_1-C_{10} alkyl.

20. An acyclovir ester as claimed in claim 19, wherein R^2 is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl.

21. L-valine alkaline salt of formula (V)

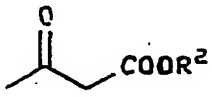


(V)

in which M is an alkali metal and R^2 is C_1-C_{10} alkyl.

22. The L-valine alkaline salt as claimed in claim 21, wherein M is selected from the group consisting of sodium and potassium, and R^2 is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl.

23. A process for preparing the L-valine alkaline salt as claimed in any of claims 21 and 22, comprising reacting L-valine in the presence of an alkaline hydroxide, with an alkyl acetoacetate of formula (VII)



(VII)

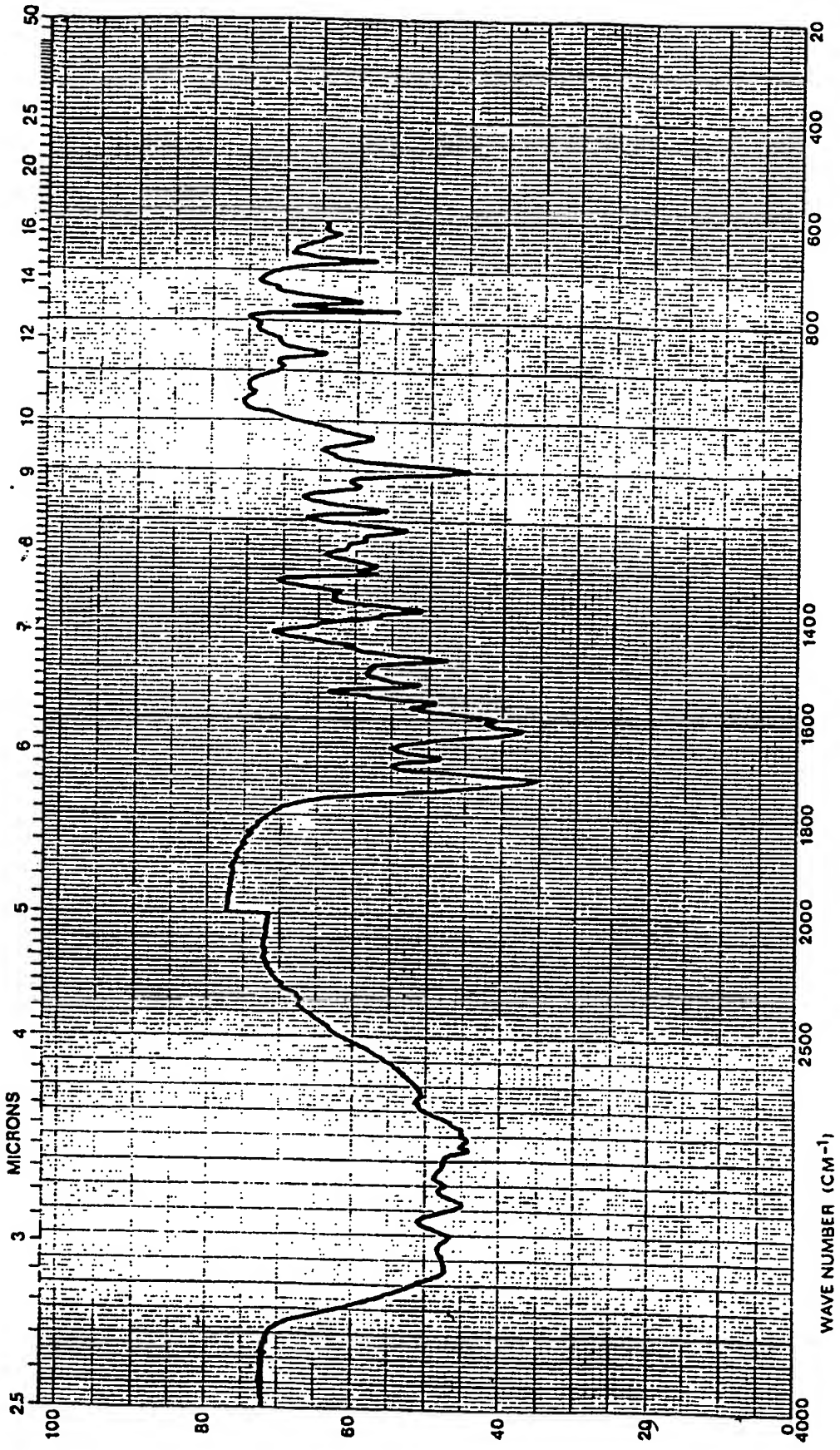
in which R^2 is C_1-C_{10} alkyl, in a solvent selected from the group consisting of an alcohol containing 1 to 4 carbon atoms, a ketone and an aromatic hydrocarbon.

an aromatic hydrocarbon.

24. The process as claimed in claim 23, wherein, when an alcoholic solvent containing 1 to 4 carbon atoms is used, said solvent is methanol.

25. The process as claimed in claim 23, wherein, when a keto solvent is used, said solvent is selected from the group consisting of methylethylketone, diethylketone, methylisobutylketone.

26. The process as claimed in claim 23, wherein, when an aromatic hydrocarbon is used as a solvent, said solvent is selected from the group consisting of toluene and xylene.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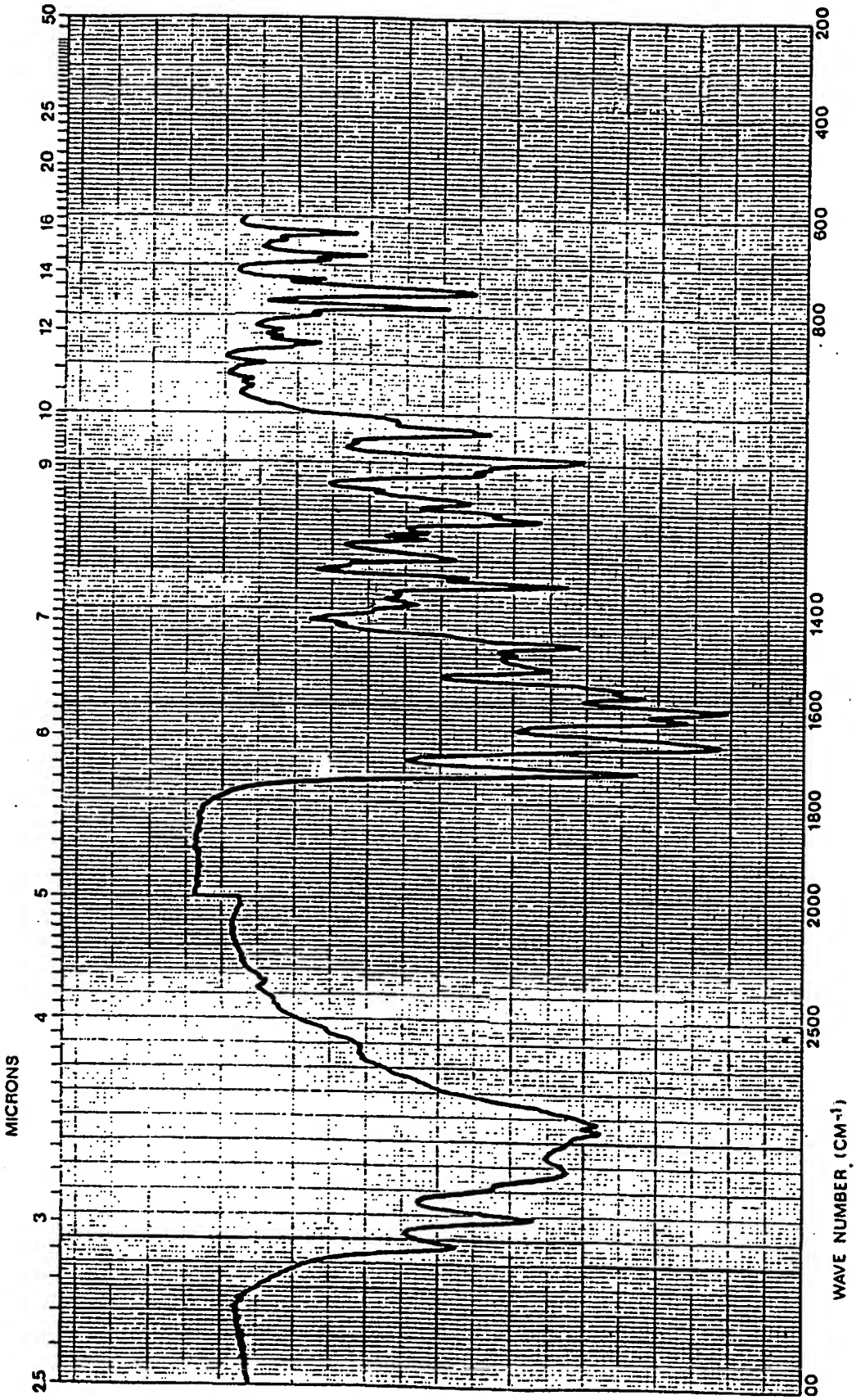
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INTERNATIONAL SEARCH REPORT

Interna. .al Application No
PCT/EP 97/03826

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D473/00 A61K31/52

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	EP 0 308 065 A (THE WELLCOME FOUNDATION LIMITED) 22 March 1989 see the whole document ---	1
A	WO 94 29311 A (FARMHISPANIA SA) 22 December 1994 see the whole document ---	1
P,A	WO 96 22291 A (THE WELLCOME FOUNDATION LIMITED) 25 July 1996 see the whole document -----	1

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Date of the actual completion of the international search	Date of mailing of the international search report
12 November 1997	21. 11. 97
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	**Authorized officer** Luyten, H

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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Internal Application No
PCT/EP 97/03826

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